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Modelling protein-DNA interactions in chromatin

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Proteins with positive charges strongly interact with DNA and, in the important cases of histones and histone-like proteins, they pack and bend long segments of DNA into highly ordered structures . In this contribution we report the results of combining numerical simulations in generalized ensembles (modulated metastatistics) with polyelectrolyte theory. The example of the interaction between the N-terminal tail of the H3 histone with segments of DNA will be illustrated, to explain the role of histone charged tails in the compaction of the genetic code in eukaryotic cells.

1 Introduction

In the eukaryotic cells, DNA is localized in the nucleus. The localization and length of the DNA filaments, require a high degree of packing for the entire genetic material. This high degree of packing also allows silencing of DNA during the cell interphase and a limited well-regulated expression of the genes[1].

The storage of DNA, that carries 2 negative charges per bp at physiological pH, in the nuclei is performed by aggregates of histone proteins, carrying a net postive charge and, therefore, attempting to form a neutral complex with DNA. The resulting complex of DNA and histone proteins is called chromatin. Each particle formed by 8 histone aggregated proteins and a portion of DNA wrapped around it is the nucleosome core particle (NCP). NCPs are linked by the non-wrapped portions of DNA called "linkers".

Only recently, the structure of chromatin has been investigated at an atomic resolution by X-ray diffraction[2] and by other techniques. The structure of highly dense chromatin is now hypothesized as a two-start helix, with the linker DNA significantly bent. The reasons of such bending has never been explored and they are the object of this study. The best candidates for the linker bending are the N-terminal tails of H3 histones: these tails are disordered and long enough to touch the linker DNA.

2 The N-terminal tail of H3 histones

The behaviour of these tails both in the absence of DNA and in the vicinity of DNA can be simulated using atomic models. First, a self-avoiding least-biased random walk[3] for a model of 25 residues moving aroung a DNA segment of 10 bp was performed. Ten different initial orientations of DNA with respect to the protein were used as ten indipendent replica. The protein was anchored at its C-terminus (residue 26) to mimick the anchoring of the N-terminal tail to the H3 rigid core.

Configurations were studied in terms of the most relevant configurational variable related to protein-DNA interactions, *i.e.* the number of electrostatic contacts, C. This quantity is defined in terms of Cζ(Arg)/Nζ(Lys) - P(DNA) distances: when this distance is lower

Z	l (bp)	R_{12} (nm)
0	0	23.5
5	4	15.2
10	8	10.2
15	13	6.8

Table 1. - Length l of bent DNA around a circle of $R = 1.5$ nm with different charge Z. R_{12} is the distance between two coplanar NCPs linked by a 65 bp linker DNA. Therefore, the first row is for a straight linker DNA.

than 0.5 nm a contact is counted. From the entire basin of configurations obtained through the random walk, 7 configurations with high ($C = 8$) and 7 with low ($C = 2$) numbers of protein-DNA contacts were immersed in a bath of water molecules and sodium counterions. These 14 systems were simulated via MD both in the presence and absence of DNA.

The results of these simulations can be summarized as in the following[6]: on average the protein increases its helical content when DNA is present in the nearby. and, consequently, the radius of gyration R is smaller ($R \sim 1$ nm) than when proteins are completely disordered or they are simulated in the absence of DNA ($R > 1.5$ nm). The MD simulations carried the protein towards configurations with about 6 protein-DNA contacts on average, irrespective of the initial number of contacts. The analysis of energetics shows that a larger number of contacts produces an increase of hydrophobic energy that may even balance the decrease of electrostatic energy. Finally, the 14 simulations of protein in the nearby of DNA did not show a specific bound configuration, rather the configurations are of different types: protein packed in the DNA major groove; protein stuck on the minor groove; protein bridging two sides of the major groove. These different configurations have similar energies.

3 The long-range bending of DNA

Once we know that the H3 N-terminal tail can be efficiently and non specifically packed by its nearby DNA, we ask if the resulting charge density (8 positive charges localized in a sphere of about 1 nm radius) can be responsible of a significant linker DNA bending.

The free energy of the protein-DNA complex can be written as a function of the length l of DNA wrapped on the protein, assuming the protein be a circle of radius R with positive charge Z. The free energy accounts fo counterion decondensation that occurs when the protein comes in contact with DNA and replaces the shell of counterions condensed by the high negative charge density of DNA[4,5]. The length of wrapped (and therefore bent) DNA is obtained by finding the minimum of the free energy. Results are summarized in Table 1, assuming the bulk salt concentration $C_s = 0.1$ M.

From these results, the answer to the question at the beginning of the section is: a charge of $+10$ confined in a region of 1.5 nm radius is able to bend 8 bp of DNA and to bring two NCPs at distances even lower than their contact distance ($R_{12} < 11$ nm).

4 Conclusions

The significant bending of linker DNA in chromatin can be performed by the N-terminal tails of H3 histones that are projected in the internucleosomal space. The extent of bending (~ 8 DNA bp) can be derived by placing a positive charge of $Z \sim 10$ within a sphere of radius $R \sim 1.5$ nm, that is similar in charge density with the collapsed H3 N-terminal tail of 25 residues as it is modelled using atoms. By using these parameters, the distance between two nucleosome core particles linked by about 65 bp of DNA (a value in the range of experimental values) are brought at contact distance and a high degree of chromatin packing is obtained only acting on the linker DNA bending. This confirms the possibility for the H3 N-terminal tail for acting as switches for keeping the chromatin dense when tails are charged, and for relaxing the structure when tails are neutralized. This latter event is actually performed by lysine acetilation due to specific enzymes and is limited to the N-terminal tails becaues of their larger accessibility compared to the histone cores.

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References

1. J. Widom, *Structure, dynamics and function of chromatin in vitro*, Ann. Rev. Biophys. Biomol. Struct. **27**, 285–327 (1998).
2. T. Schalch, S. Duda, D. F. Sargent, and T. J. Richmond, *X-ray structure of a tetranucleosome and its implications for the chromatin fibre*, Nature **436**, 138–141 (2005).
3. G. La Penna, S. Morante, G. C. Rossi, and A. Perico, *Designing generalized statistical ensembles for numerical simulations of biopolymers*, J. Chem. Phys. **121**, 10725–10741 (2004).
4. G. S. Manning, *Is a small number of charge neutralizations sufficient to bend nucleosome core DNA onto its superhelical ramp?* J. Am. Chem. Soc. **125**, 15087–15092 (2003).
5. A. Perico, G. La Penna, and L. Arcesi, *Electrostatic interactions with histone tails may bend linker DNA in chromatin*, Biopolymers **81**, 20–28 (2006).
6. G. La Penna, S. Furlan, and A. Perico, *Modelling H3 histone N-terminal tail and linker DNA interactions*, Biopolymers , to be published (2006).